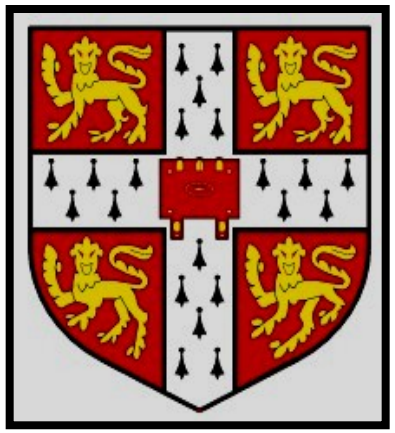
Non Mendelian Inheritance

Patterns of inheritance in which traits do not segregate in accordance with Mendel's laws

Evidence for Genomic Imprinting



Claire Quilter: crq20@cam.ac.uk

Non-Mendelian inheritance - any pattern of inheritance in which traits do not segregate in accordance with Mendel's laws

- Mendel's laws describe the inheritance of traits linked to single genes on chromosomes with each parent contributing one of two possible alleles for a trait.

- If the genotypes of both parents in a genetic cross are known, Mendel's laws can be used to determine the distribution of phenotypes expected for the population of offspring.

- One allele can influences the chance of inheriting others, degrees of dominance and recessiveness.

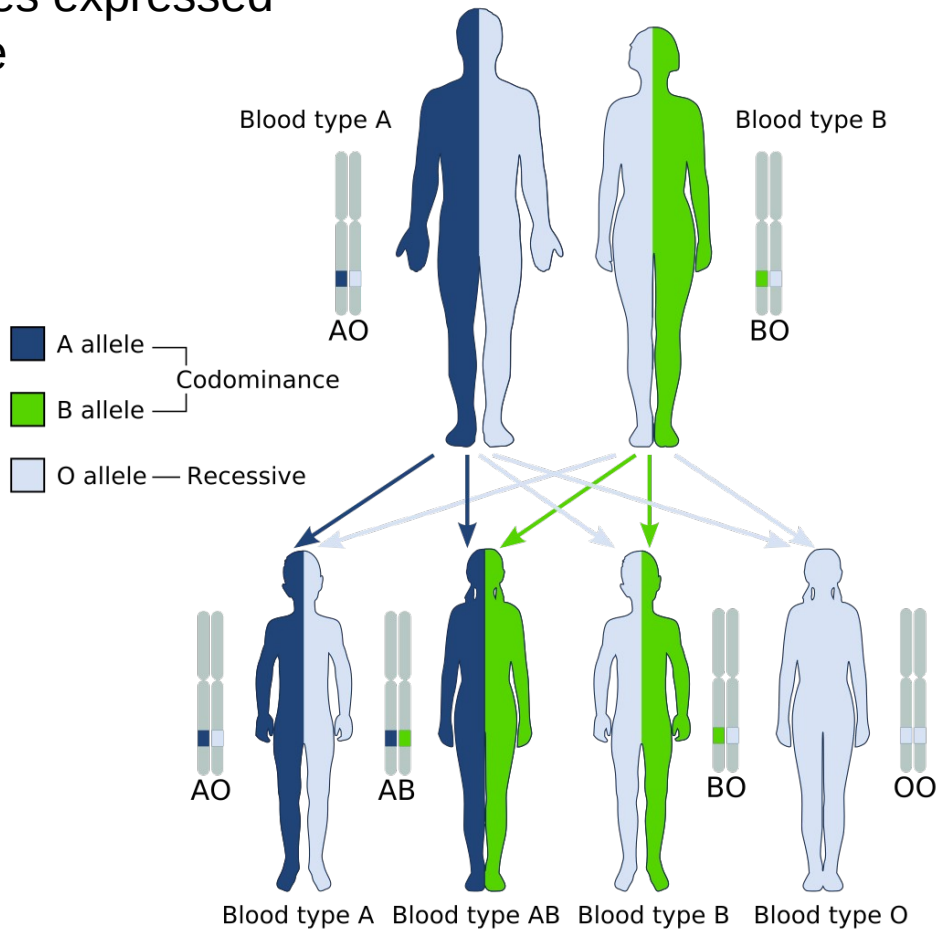
Types

- Co-dominance
- Allele exclusion
- Extra nuclear inheritance
- Gene conversion
- Mosaicism
- Triplet repeat disorders
- Lamarckian inheritance
- Transgenerational transmission of epigenetic traits
- Genomic imprinting

Two alleles are dominant - A and B
O is recessive

Both phenotypes expressed
in heterozygote

Co - dominance



Co-dominance occurs when the contributions of both alleles are visible in the phenotype.

Blood phenotype	Blood genotype
A	AA or AO
B	BB or BO
AB	AB
O	OO

Co dominance

- Both alleles expressed in heterozygote
- Both contribute to phenotype
- The two alleles don’t blend but rather are both present in the offspring
- Other examples are roan horses, checkered chickens, roan cattle

Codominance

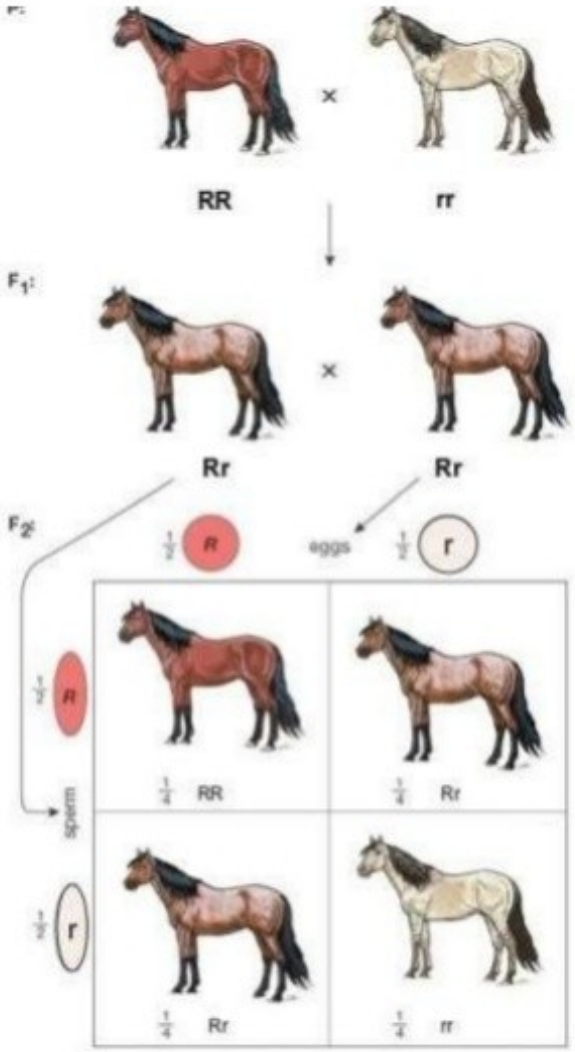
Black

White

Checkered

Black chicken

White chicken	B	B
W	**BW** Checkered	**BW** Checkered
W	**BW** Checkered	**BW** Checkered



Roan Horse

http://search.vadlo.com/b/q?rel=2&keys=Dominance+Incomplete+Dominance+Codominance+PPT

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Allele exclusion

- Allele exclusion is a process by which only one allele of a gene is expressed while the other allele is silenced.

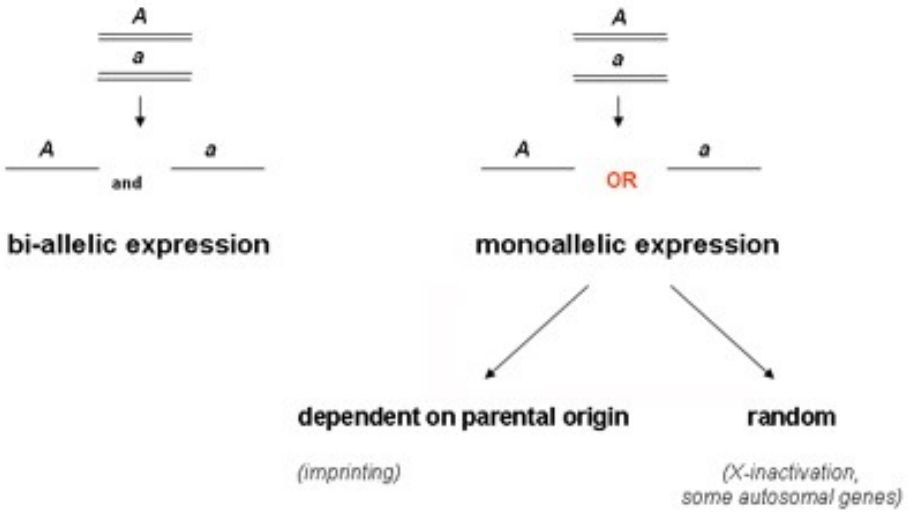
- At least two distinct selection events can lead to allelic exclusion:

  - one allele of the gene can be transcriptionally silent, which would result in the expression of only the second allele.

  - both alleles can be transcribed, in which case post-transcriptional and post-translational mechanisms will lead to the elimination of the

Allele exclusion

- Mono-allelic gene expression is a general phenomenon critical for normal biology.
- Important in genetic imprinting and X chromosome inactivation, enforcing gene silencing in all cell types. Defects cause human disorders

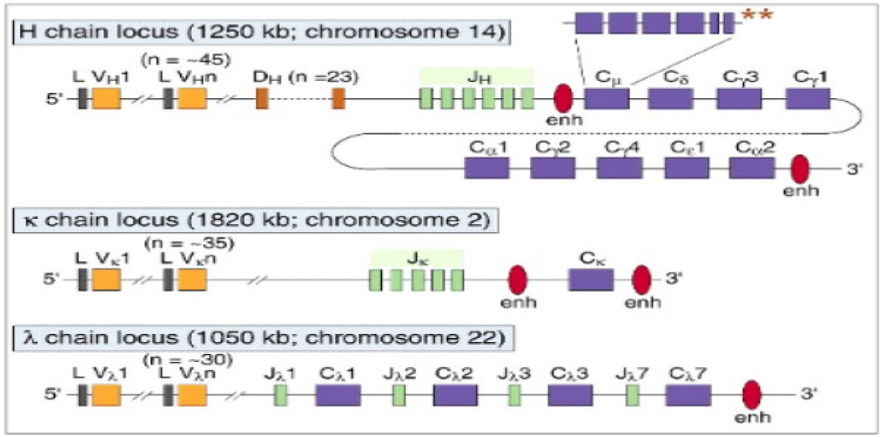


Antigen receptor allele exclusion

- Most lymphocytes express cell surface antigen receptor chains from single alleles of distinct immunoglobulin (Ig) or T-cell receptor (TCR) loci.
- 3 Ig genes per haploid chromosome set so 6 available to diploid B cells making Ig chains.
- B cell is monospecific – ie it only produces one type of Ig with a single type of heavy chain and a single type of light chain

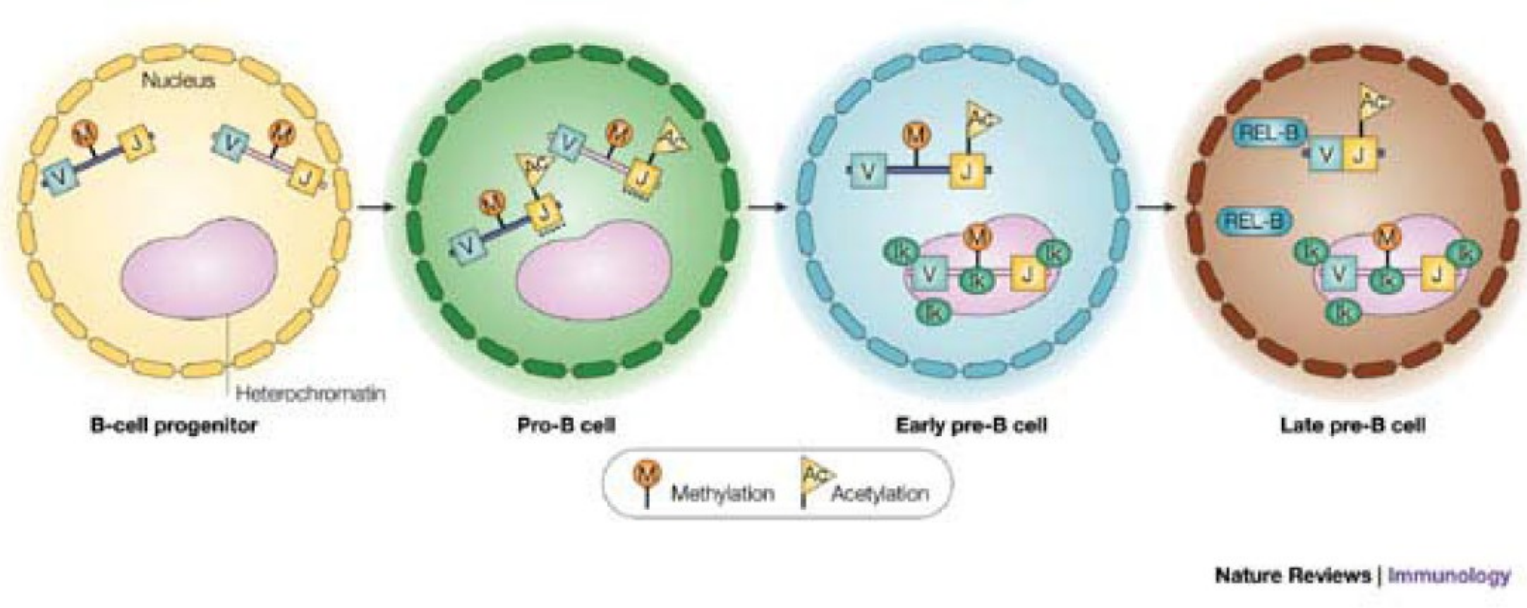
Brady et al. (2011) Antigen Receptor Allelic Exclusion: An Update and Reappraisal. J Immunol: 185(7): 3801-3808.

Immunoglobulins (Igs)



- Allelic exclusion –light chain or heavy chain from a mat or pat chromosome in any one B cell but not both -monoallelic expression at the heavy chain locus in B cells.
- Also light chain exclusion - a light chain is synthesized in a single B cell may be a κ chain or a λ chain but never both- monoallelic expression of one of two functional light chain gene clusters and no expression at the other.

Possible mechanism for allele exclusion



Nature Reviews Immunology 4, 753-761 (October 2004) | doi:10.1038/nri1458

A stepwise epigenetic process controls immunoglobulin allelic exclusion

Yehudit Bergman[1] and Howard Cedar[1]

Allele exclusion – Olfactory receptors

- Olfactory receptors largest gene family in humans and mice.
- Competition for a single – copy enhancer.
- Each olfactory neuron expresses just one single allele of a single receptor gene so fires only in response to a single odorant.
- Expression of an olfactory receptor depends on a single copy of an enhancer sequence in each genome.
- In mice the single copy enhancer can associate with any of 1300 receptor genes.
- A diploid olfactory neuron has two copies of the enhancer sequence but only one is active. Other inactivated by methylation (CpA rather than CpG) – allele exclusion.

Lomvardas S, Barnea G, Pisapia DJ, Mendelsohn M, Kirkland J, Axel R. Interchromosomal

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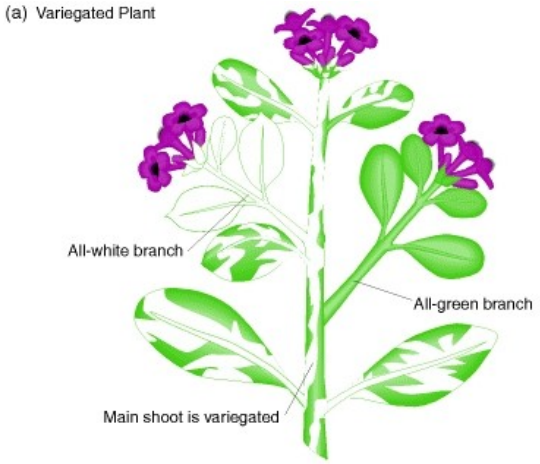
Extranuclear Inheritance

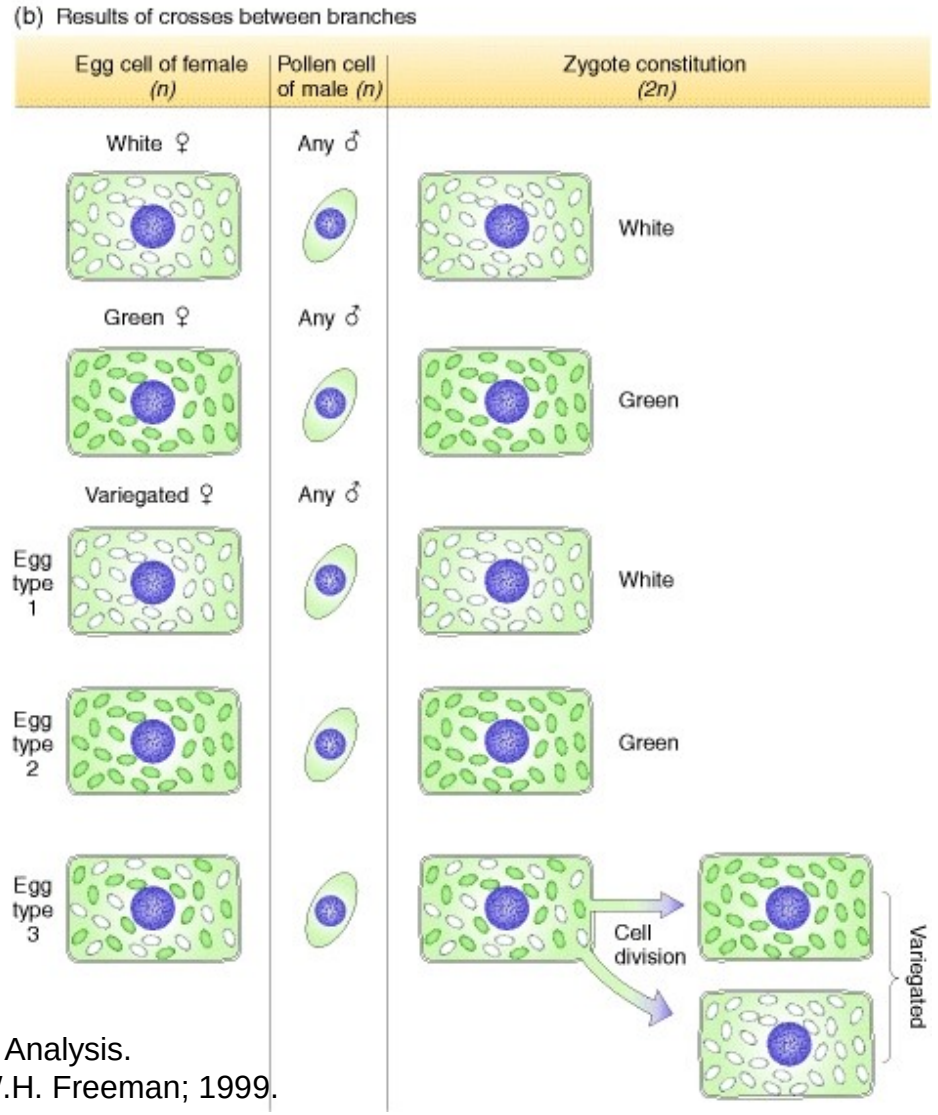
- Cytoplasmic inheritance
- The transmission of genes that occur outside the nucleus.
- It is found in most eukaryotes and is commonly known to occur in cytoplasmic organelles such as mitochondria and chloroplasts or from cellular parasites like viruses or bacteria.
- Cytoplasmic inheritance, discovered by Carl Correns(1908) from work on *Mirabilis jalapa.*
- Leaf colour dependant on maternal genotype, trait was
  transmitted through a character present in the cytoplasm of the ovule – later found to be DNA in chloroplasts

Extranuclear Inheritance



Leaf variegation in *Mirabilis jalapa,* the four-o'clock plant.

Flowers may form on any branch (variegated, green, or white), and these flowers may be used in crosses.



From: Inheritance of Organelle Genes Modern Genetic Analysis.
Griffiths AJF, Gelbart WM, Miller JH, et al. New York: W.H. Freeman; 1999.

Extranuclear Inheritance

- Poky strain of mould *Neurspora crassa*- genetic material in mitochondria, first isolated by Mitchell and Mitchell (1952).
  - A poky mutant differs from wild type strain of Neurospora in the following aspects:
  - (1) it is slow growing;
  - (2) it shows maternal inheritance, and
  - (3) it has abnormal cytochromes - cyt a, b and c found in wild type, cyt a and cyt b are absent, and cyt c is in excess in poky mutant.

Poky (female) × wild type (male) → all poky

Wild type (female) × poky (male) → all wild type

- Other marker nuclear genes show 1:1 Mendelian segregation suggested that poky trait may be located in mitochondrial DNA: (i) slow growth may be due to lack of ATP energy and source of this energy is mitochondria; (ii) cytochromes in poky strain differ from those in wild type in quality and quantity and these cytochromes are found in mitochondria.
- Both present in the cytoplasm of maternal gametes only so phenotype linked to genes determined exclusively by the maternal parent.
- Endosymbiont theory - Mitochondria and Chloroplasts were free living

Mitochondrial disease

- In humans, mitochondrial diseases are a class of diseases:
  - Major contributor of ATP, via oxidative phosporylation (OXPHOS).
  - Mitochondrial diseases as a rule are worse when the defective mitochondria are present in the muscles, cerebrum or nerves (cells use more energy).

- Mitochondrial diseases in humans:
  - Neuromuscular (mitochondrial myopathy).
  - Eye (Leber’s hereditary optic neuropathy).

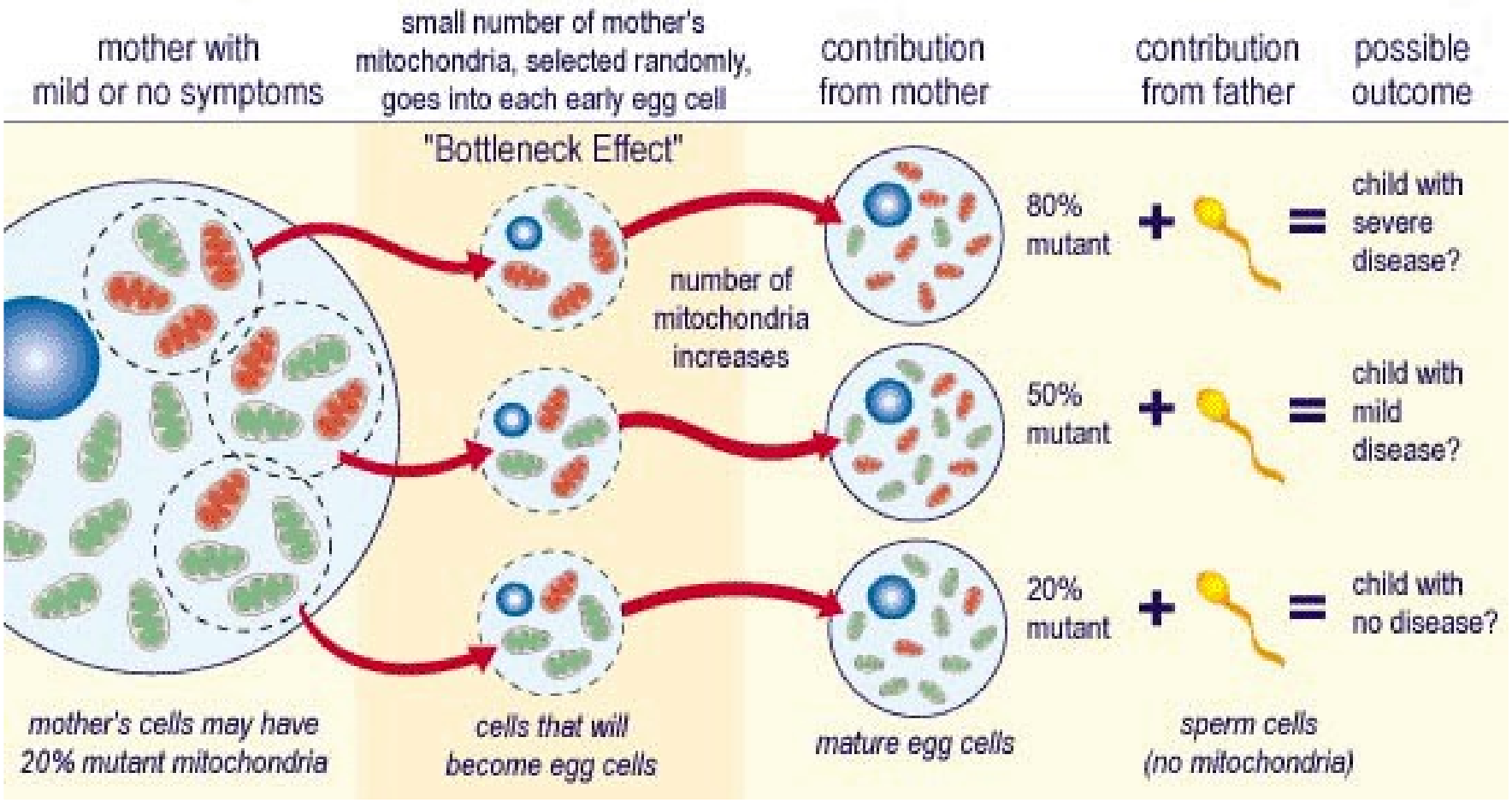
Mitochondrial disease

- During cell division the mitochondrial DNA (mtDNA) copies segregate randomly between the two new mitochondria, and then those new mitochondria make more copies.

- If only a few of the mtDNA copies inherited from the mother are defective, mild disease manifests but if mitochondrial division cause most of the defective copies to end up in just one egg more severe disease.

- Mt inheritance can mask the chromosomal inheritance.

Mitochondrial disease

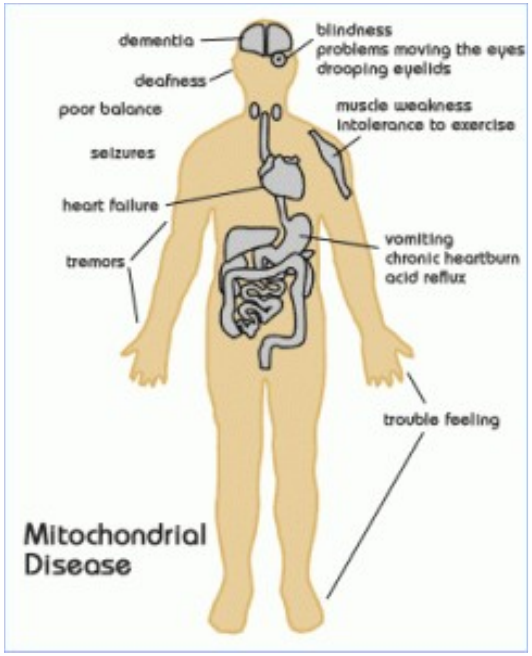


http://www.mda.org/disease/mitochondrial-myopathies/causes-inheritance

Mitochondrial disease

- Clinical symptoms heterogeneous.
- Further complicated by dual genomic expression of mitochondrial proteins from both nuclear and mitochondrial DNA (mtDNA).
- Homoplasmy (when only mutant mtDNA is present) – identical, clonal.
- Heteroplasmy – both mutated and wild type mtDNA molecules co-exist in a cell.

Mitochondrial disease



- General Symptoms: poor growth, loss of muscle coordination, muscle weakness, visual problems, hearing problems, learning disabilities, mental retardation, heart disease, liver disease, kidney disease, gastrointestinal disorders, respiratory disorders, neurological problems, and dementia

Esposito LA, Melov S, Panov A, Cottrell BA, Wallace DC. Mitochondrial disease in mouse results in increased oxidative stress. Proc Natl Acad Sci U S A. 1999 Apr 27;96(9):4820-5. PubMed PMID: 10220377; PubMed Central PMCID: PMC21775.

Uk

- Overrepresented Longevity (99, 100)
- Breast cancer (75)
- LHON (44)
- ARHL (47)

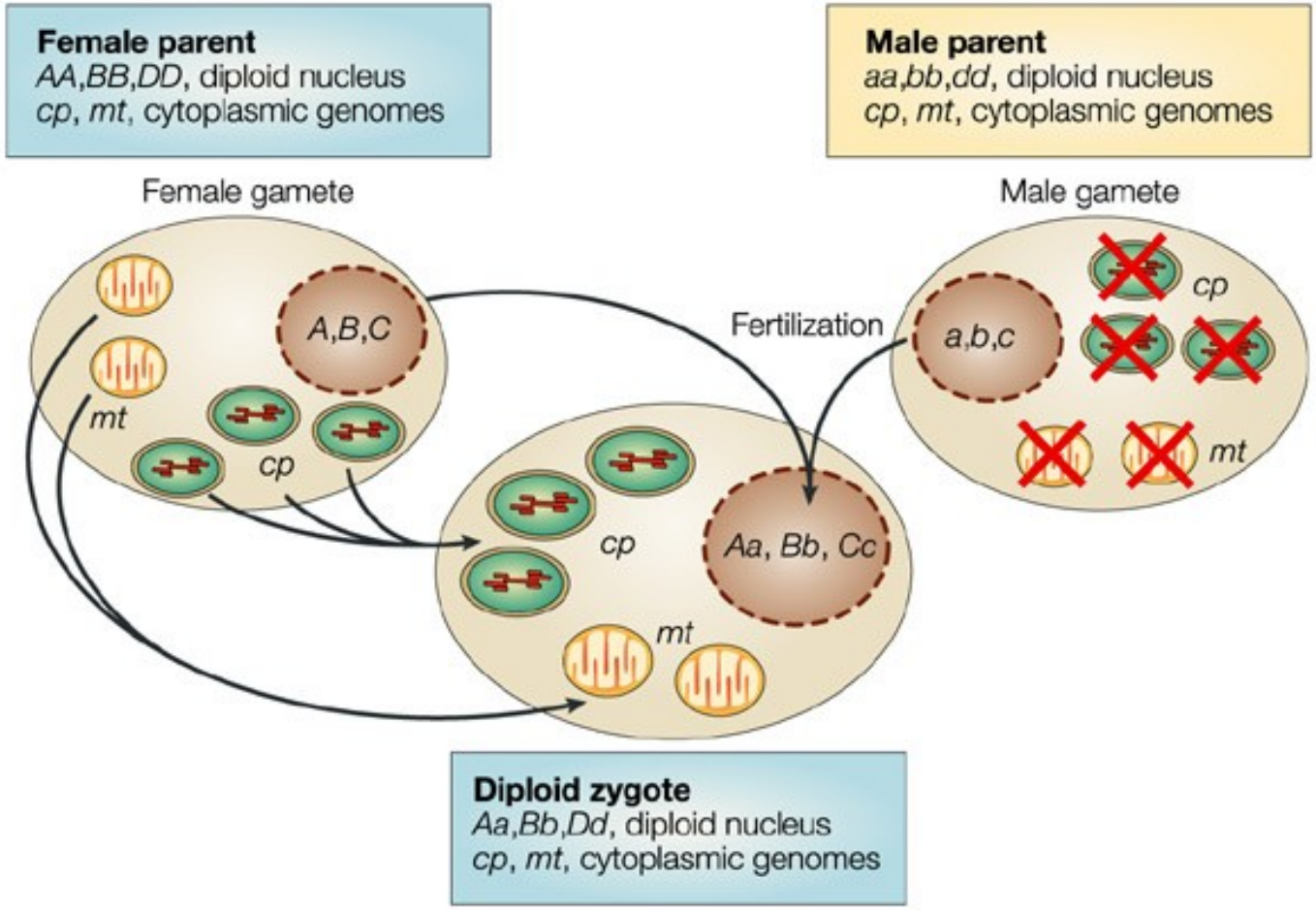
H

- Overrepresented Sperm motility (88)
- Sepsis (80)
- ND (PD, AD) (11, 23)

LHON, ARHL, FAP, ND (PD, AD), CIVE indicate the following:

Leber's hereditary optic neuropathy, age-related hearing loss, familial amyloidosis with polyneuropathy, neurodegenerative diseases (Parkinson's disease, Alzheimer's disease) and cerebral ischemic vascular events. Gómez-Durán et al. (2010) *Hum Mol Genet.* ;19(17):3343-53. doi: 10.1093/hmg/ddq246.

Extranuclear Inheritance



Nature Reviews | Genetics

Types

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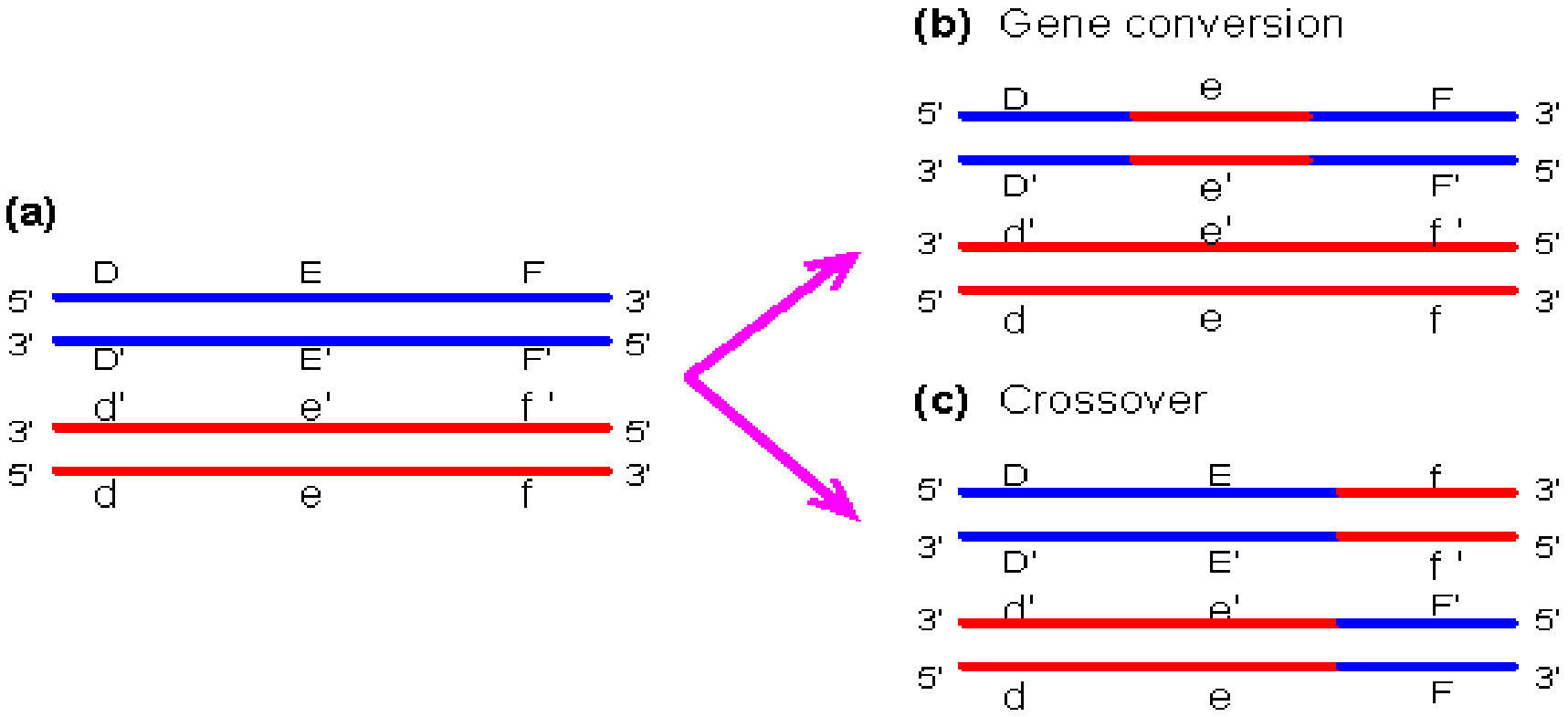
Gene conversion

- **Gene conversion** is an event in DNA genetic recombination - occurs at high frequencies during meiotic division but which also occurs in somatic cells (mitosis).

- It is a process by which DNA sequence information is transferred from one DNA helix (which remains unchanged) to another DNA helix, whose sequence is altered.

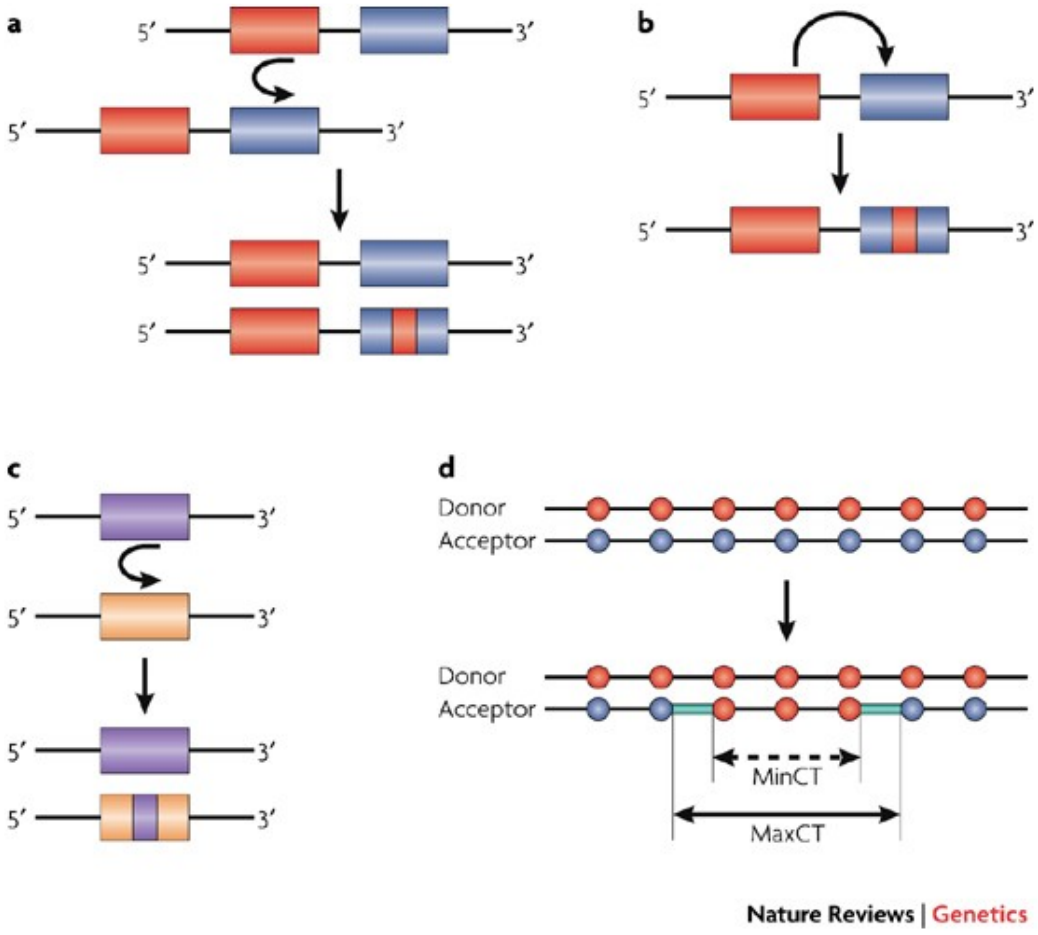
- Repetitive DNA sequences in gene regions – non homologous recombination between homologous chromosomes - disease – However also misalignment on paired chromatids – nonreciprocal sequence exchange – one sequence unchanged other mutated.

Difference between gene conversion and cross overs



Gene conversion is a nonreciprocal transfer of genetic information - mutation of the *CYP21A2* gene is a common underlying genetic cause of a subform of congenital adrenal hypoplasia.

Gene conversion mechanisms



Chen JM, et al. Gene conversion:mechanisms, evolution and human disease. Nat Rev Genet. 2007 Oct;8(10):762-75. Review. PubMed PMID: 17846636.

a | Non-allelic (or interlocus) gene conversion in trans, shown as an event occurring between paralogous sequences (represented as red and blue boxes) that reside on sister chromatids or on homologous chromosomes. Gene-conversion events that occur between homologous sequences that reside on different chromosomes are not shown.

b | Non-allelic gene-conversion events in cis (between non-allelic gene copies that reside on the same chromosome). Gene-conversion events, which are depicted in a and b, are virtually indistinguishable from each other.

c | Interallelic gene-conversion events occurring between alleles (shown in purple and orange) on homologous chromosomes.

d | Maximal and minimal converted tracts of a given gene-conversion event. Although the length of the minimal converted tract (MinCT) is usually shorter than the true tract, the length of the maximal converted tract (MaxCT) is usually longer than the true tract. The initiating and terminating points of gene conversion can lie anywhere within the two

Interlocus gene-conversion events that cause inherited disease

Disease/phenotype	Donor gene	Acceptor gene	Chromosomal localization	Directional -ity	Converted tract length (bp)
Congenetal adrenal hyperplasia	CYP21A1P	CYP21A2	6p21.3	5'>3'	various - different mutations
Syndrome of corticosterone methyloxidase II deficiency	CY11B1	CY11B2	8q21-q22	3'>5'	446-626
Autosomal dominant cataract	CRYBP1	CRYBB2	22q11.2-q12.1	3'>5'	9-104
Gaucher disease	GBAP	GBA	1q21	3'>5'	various - different mutations
Short stature	GH2	GH1	17q22-q24	3'>5'	40-218

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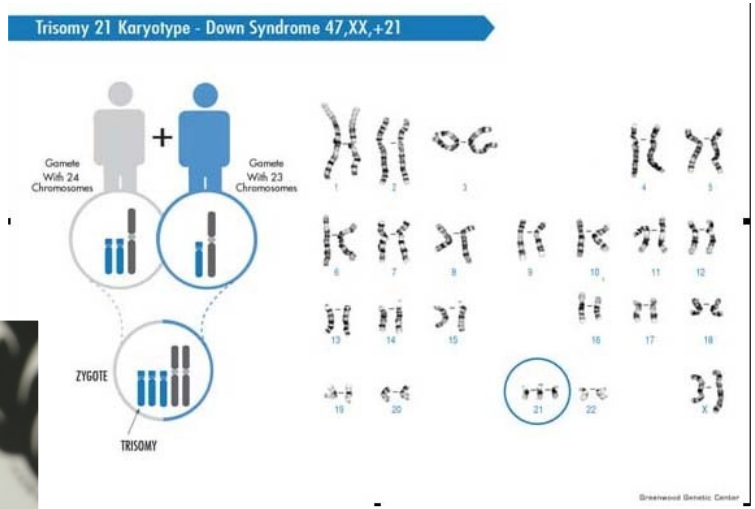
Mosaicism

- Mutation that is acquired in some somatic tissues AFTER fertilisation - results in only some cells of the body being affected.
- Essentially two or more genotypes.
- Most chromosome trisomies: Downs, Edwards, Patau syndromes.
- Sex chromosome mosaicism: Turner, Klinefelter syndrome.
- Milder phenotypes.

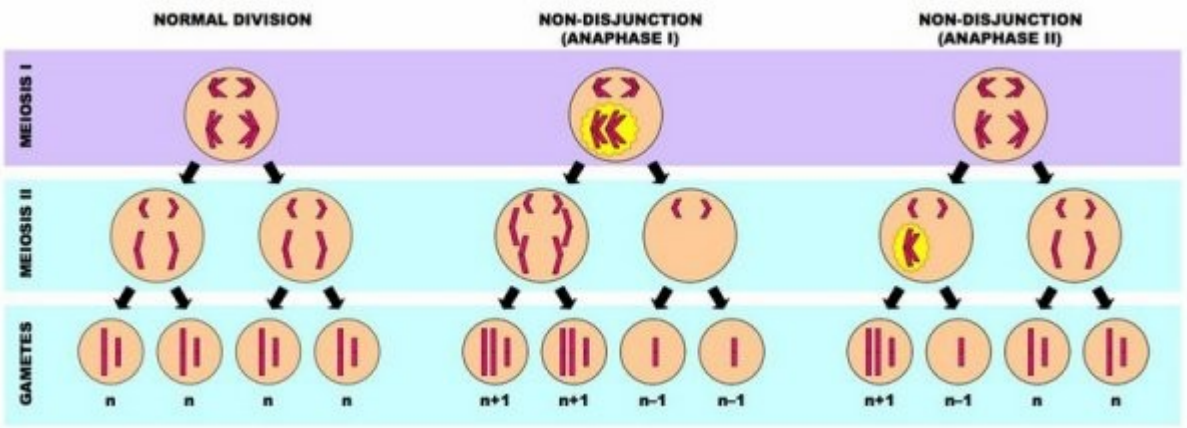
Mosaic Down Syndrome

47,XX,+21

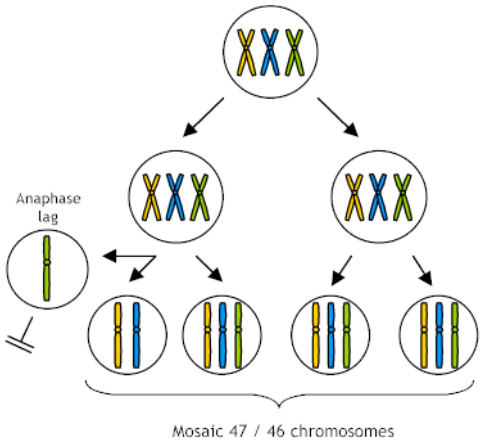


46, XX/47,XX,+21

Mosaic trisomies



Non - disjunction in meiosis to give gamete with an extra chromosome



Mitotic non-disjunction in trisomy embryo

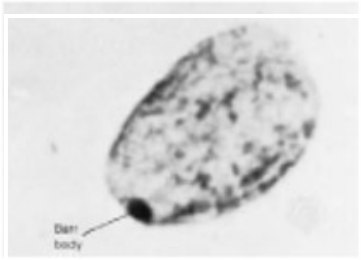
Mosaic Sex Chromosome disorders

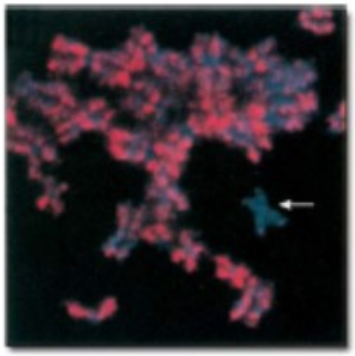
- Turner's – 45,X/46,XX, 45,X/46Xi(Xq), 45,X/r(X), 45,X/46,X,del(X), 45,X/46,XY
  - All TS patients mosaic?
  - X inactivation of abnormal X - genes that escape X inactivation – candidates.
  - short stature, infertility, osteoporosis, high blood pressure, kidney abnormalities, hypothyroidism.
  - Ring/marker chromosomes – small, severe phenotype no *XIST*.
- Klinefelter's 45,X/46,XY/47,XXY
  - Spermatogenesis.
- Gonadal mosaicism.

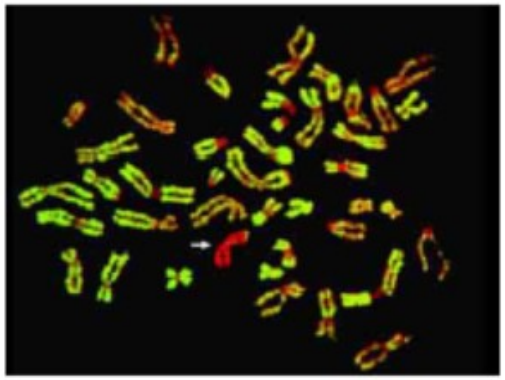
X inactivation

- In embryogenesis cells count how many X chromosomes and then permanently inactivate all except one randomly selected X.
- Early stages both X’s active, X-inactivation as cells differentiate – last blastula stage in mice.
- Inactive X remains in remain in a highly condensed heterochromatic state

X inactivation







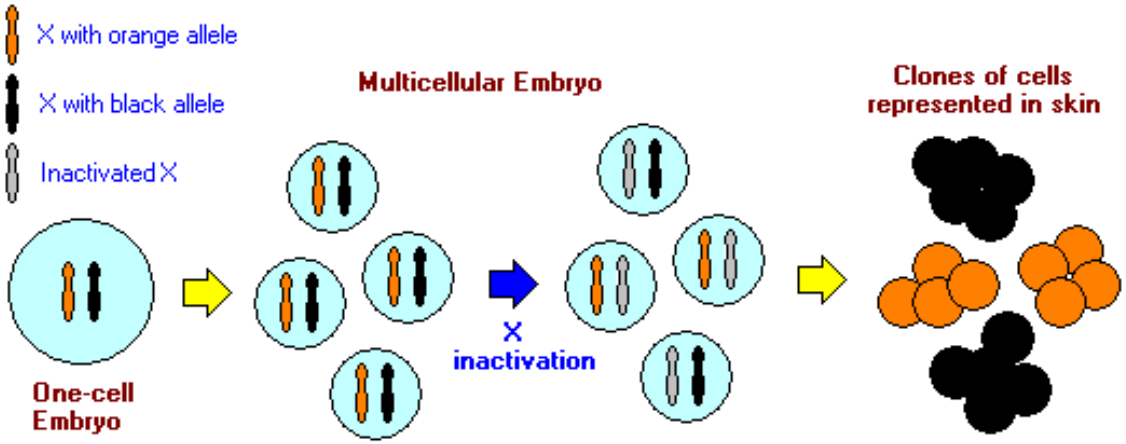
Barr Body

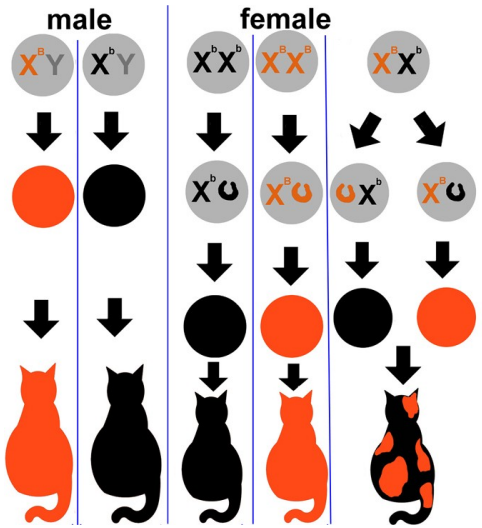
Chromosome staining showing inactive X

X inactivation

- Random inactivation of one X
  - except mice and marsupials – paternal X consistently inactivated.
  - extends to mouse placenta.
- Same X inactivated in all daughter cells.
- Adult female mosaic of cell clones – each cell clone retaining pattern of X-inactivation established in progenitor cell early in embryo – tortoiseshell cat.
- Stable through mitosis (not generations).

Genetics of the Tortoiseshell Cat

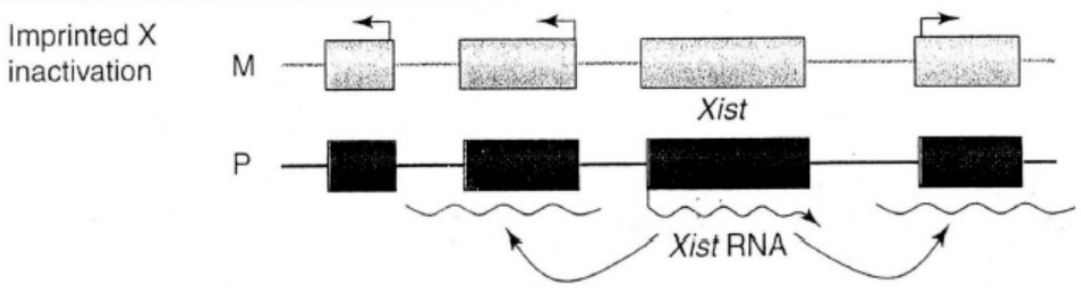




http://www.vivo.colostate.edu/hbooks/genetics/medgen/chromo/mosaics.html

XIST

- Inactivation initiated at XIC (Xq13) -heterochromatin spreading.
- Pairing of XIC – counting mechanism.
- Inactivation - expression of *XIST* only from inactive X – encodes large ncRNA – si ons.



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Trinucleotide repeat disorders

- Disorders caused by the expansion of microsatellite tandem trinucleotide repeats (TNRs) – intergenic, introns, untranslated regions or in exons.

- In normal individuals, n(repeats) is relatively low <30. With each successive generation, there is a chance that the n(repeats) will expand and get worse - anticipation.

- Abnormal expansions can result in disease. Progeny can progress from pre-mutation (carriers) to affected status.

Why 3 nucleotides?

- TNR expansions tend to be near coding regions of the genome, caused by *slippage* during DNA replication.

- Mutations of 3 base pairs, do not cause a catastrophic frameshift mutation unless a stop codon (TAG, TAA, TGA) is the triplet that is added to the gene - which would in almost all cases render the protein coded useless.

- So trinucleotide addition to a gene can have no effect at all on the protein, can cripple the protein, or sometimes make it work even better.

Trinucleotide repeat disorders

- Largest group polyglutamine (polyQ) disorders -expansion of CAG repeats in ORF of unique genes - Huntington's disease (HD) and Spinocerebellar Ataxia (SCA).

- HD -motor, cognitive and psychiatric disturbances – exact mechanism how expanded repeat causes disease progression not understood, more repeats earlier onset.

- Hypothesis is expanded polyQ track confers detrimental properties to the HTT protein, compromises cell homeostasis.

Classification of the trinucleotide repeat and disease status in Huntingdon's Disease

- CAG repeats

Repeat count	Classification	Disease status
<28	Normal	Unaffected
28–35	Intermediate	Unaffected
36–40	Reduced Penetrance	+/- Affected
>40	Full Penetrance	Affected

Polyglutamine (PolyQ) Diseases

Type	Gene	Normal	Pathogenic
DRPLA (Dentatorubropallidoluysian atrophy)	ATN1 or DRPLA	6 - 35	49 - 88
HD (Huntington's disease)	HTT (Huntingtin)	10 - 35	35+
SBMA (Spinobulbar muscular atrophy or Kennedy disease)	Androgen receptor on the X chromosome.	9 - 36	38 - 62
SCA1 (Spinocerebellar ataxia Type 1)	ATXN1	6 - 35	49 - 88
SCA2 (Spinocerebellar ataxia Type 2)	ATXN2	14 - 32	33 - 77
SCA3 (Spinocerebellar ataxia Type 3 or Machado-Joseph disease)	ATXN3	12 - 40	55 - 86
SCA6 (Spinocerebellar ataxia Type 6)	CACNA1A	4 - 18	21 - 30
SCA7 (Spinocerebellar ataxia Type 7)	ATXN7	7 - 17	38 - 120
SCA17 (Spinocerebellar ataxia Type 17)	TBP	25 - 42	47 - 63

Non-Polyglutamine Diseases

- Fragile X syndrome - CGG >200, the most common type of mental retardation, also autism - affects *FMR1* gene – abnormal protein.
- Increased methylation (epigenetic) - reduced expression of the fragile X mental retardation gene (FMR1) in individuals with a sufficient number of repeats.
- 55-200 repeats– Fragile X tremor/ataxia syndrome, POF.
- CCG FRAXE.
- Large expansions in non-translated regions – produce RNAs with toxic gain.

Non-Polyglutamine Diseases

Type	Gene	Codon	Normal/ wildtype	Pathogenic
FRAXA (Fragile X syndrome)	*FMR1*, on the X-chromosome	**CGG**	6 - 53	230+
FRAXE (Fragile XE mental retardation)	AFF2 or FMR2, on the X-chromosome	**GCC**	6 - 35	200+
FRDA (Friedreich's ataxia)	FXN	**GAA**	7 - 34	100+
DM (Myotonic dystrophy)	DMPK	**CTG**	5 - 37	50+
SCA8 (Spinocerebellar ataxia Type 8)	OSCA or SCA8	**CTG**	16 - 37	110 - 250
SCA12 (Spinocerebellar ataxia Type 12)	PPP2R2B or SCA12	**CAG** On 5' end	7 - 28	66 - 78

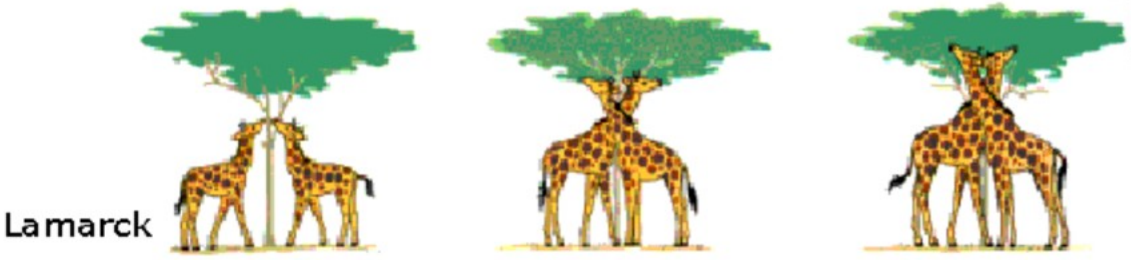
Types

- Co-dominance
- Allele exclusion
- Extra nuclear inheritance
- Gene conversion
- Mosaicism
- Triplet repeat disorders
- **Lamarckian inheritance**
- Transgenerational transmission of epigenetic traits
- Genomic imprinting

Lamarckian inheritance

Lamarckian inheritance is a synonym for the idea of the inheritance of acquired characters named after the French biologist Jean-Baptiste Lamark (1744-1829).

Lamarck



Darwin

Types

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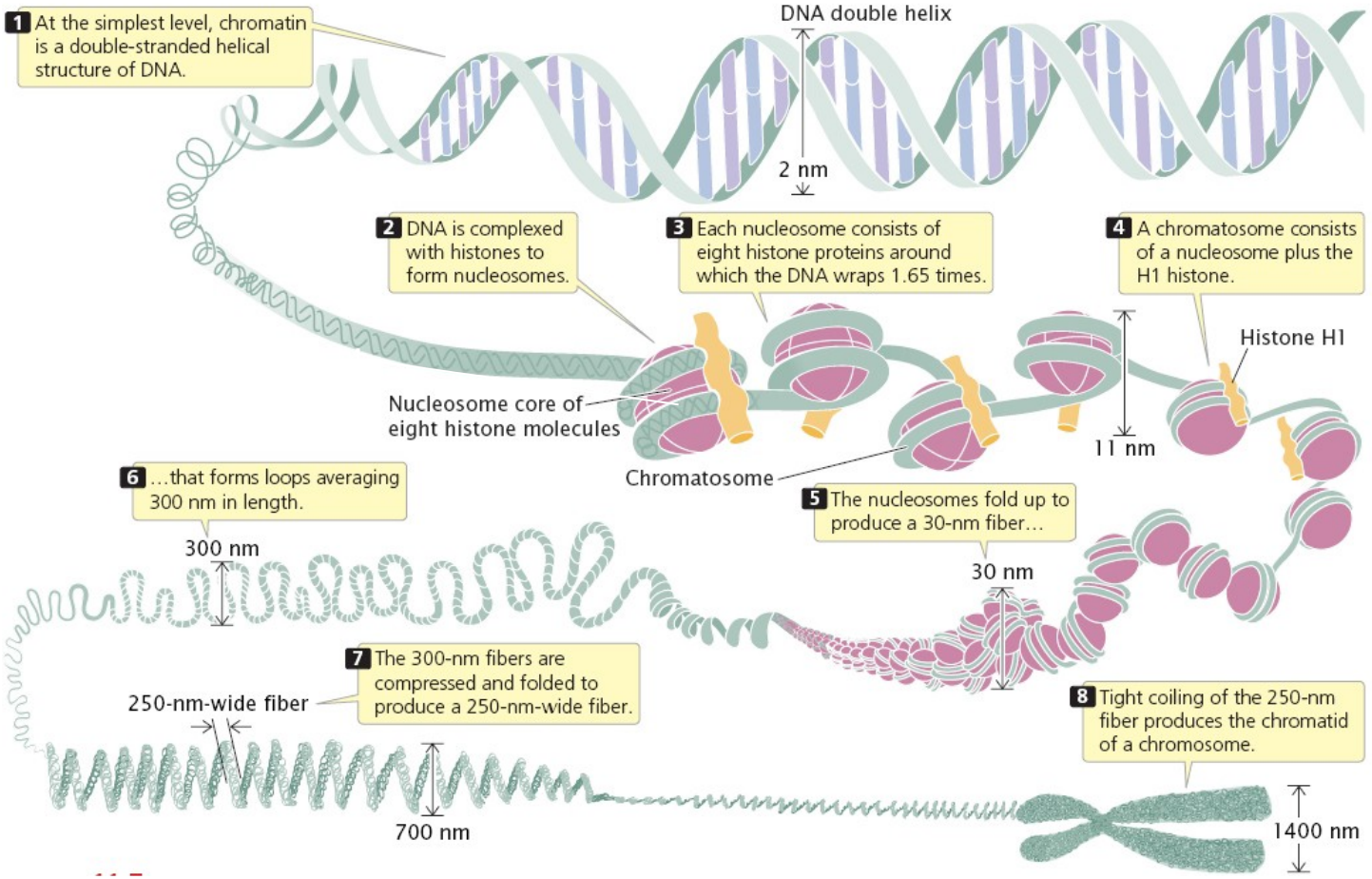
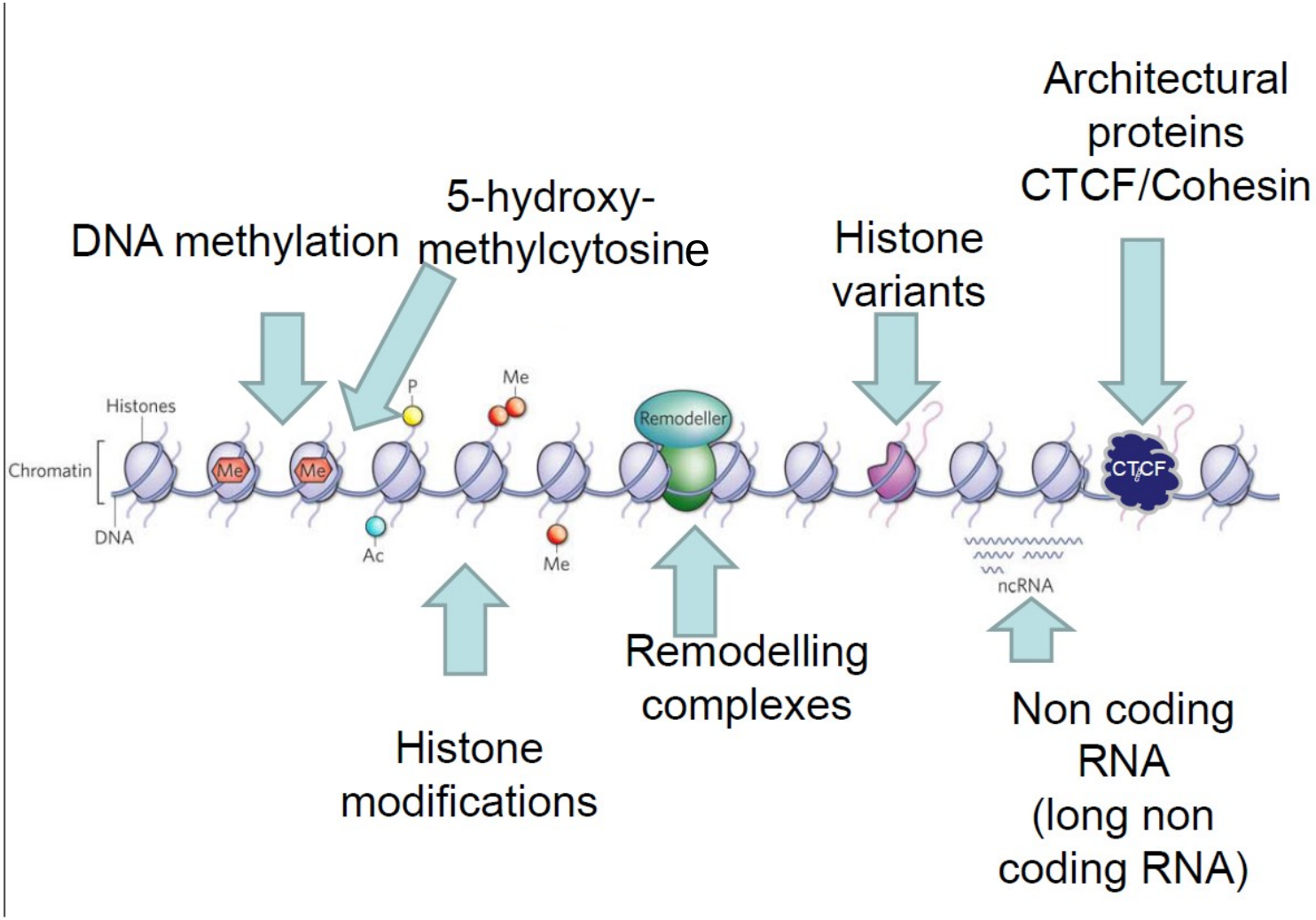
- **Transgenerational transmission of epigenetic traits**
- Genomic imprinting

- The study of changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence.
- *epi-* (Greek: *επί-* over, above) - *genetics*.
- Cellular differentiation – all cells have same genetics but have variation in phenotypes.

Chromatin structure



Epigenetic processes provide a mechanism for environmental factors to modulate gene activity.

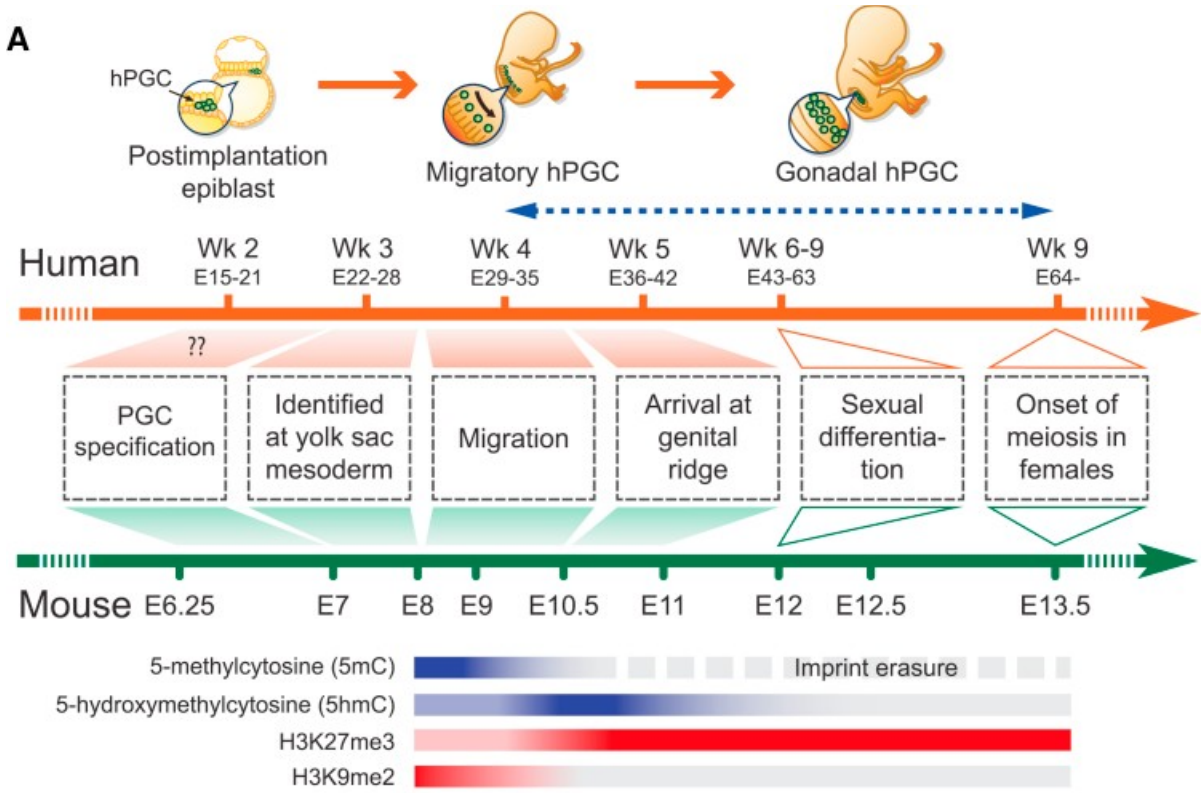


Epigenetic inheritance

- Early life is a time of developmental plasticity
  - Non-genetic environmental factors - smoking, diet, stress.
  - Adverse pre-natal environments can promote metabolic disease in offspring and subsequent generations.

- Bodies adapt - adult health onset disease
  - Metabolic disease increasing globally.
  - Cardiovascular.

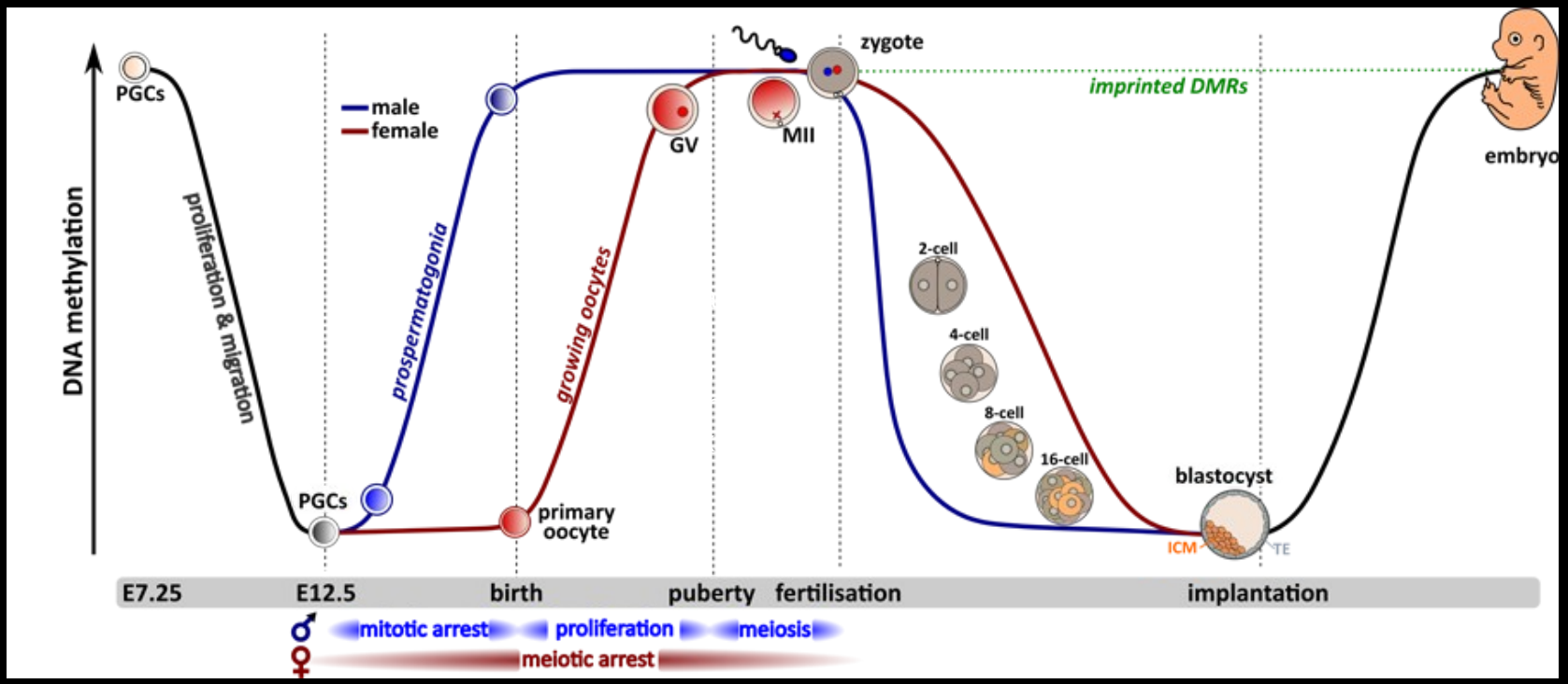
  For epigenetic inheritance has to reach F2 offspring.



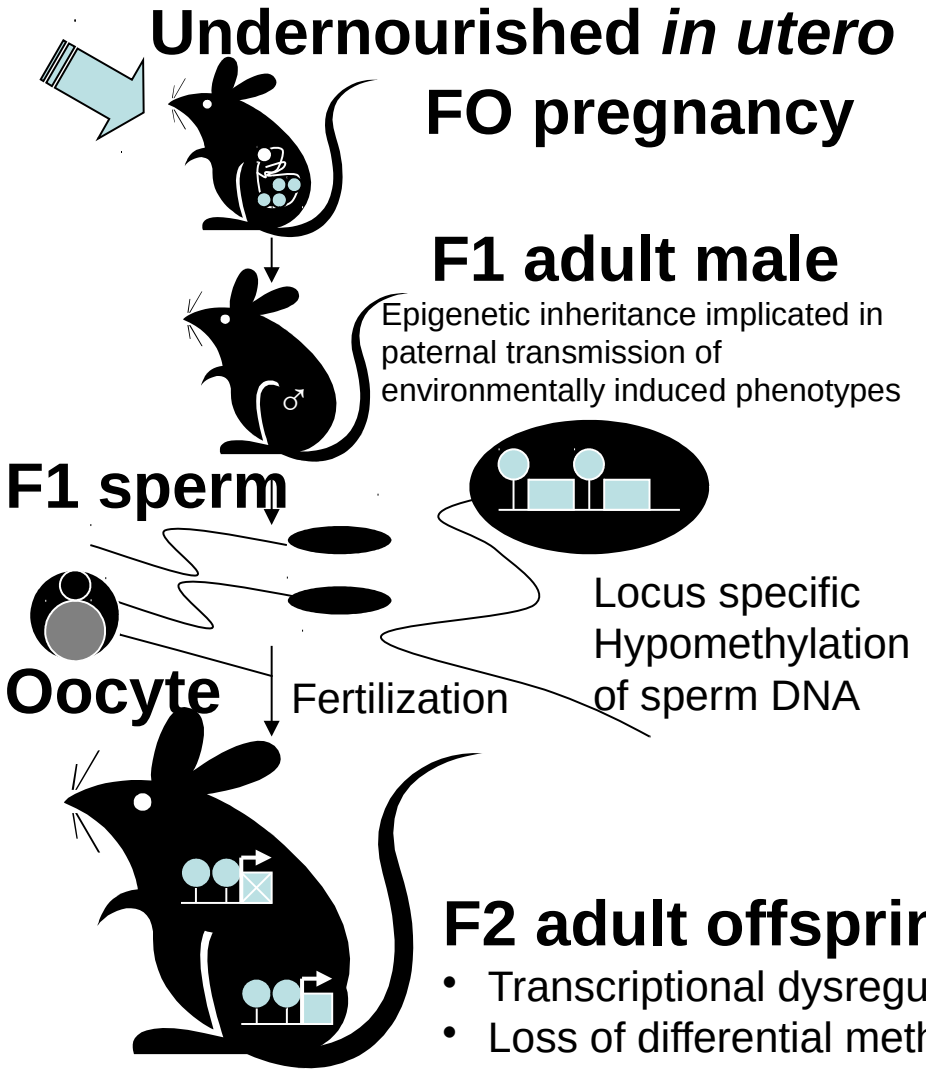
- PGS epigenome erased prior to sperm/ egg generation weeks 2-9
- 5% DNA escapes reprogramming – neuronal genes important in development but may also be involved in schizophrenia, metabolic disorders and obesity.
- Retroelements – beneficial/detrimental. Some also escape.

Tang WW, Dietmann S, Irie N, Leitch HG, Floros VI, Bradshaw CR, Hackett JA, Chinnery PF, Surani MA. A Unique Gene Regulatory Network Resets the Human Germline Epigenome for Development. Cell. 2015 Jun 4;161(6):1453-67. doi: 10.1016/j.cell.2015.04.053. PubMed PMID: 26046444; PubMed Central PMCID: PMC4459712.

Methylation during germ cell development



In utero undernourishment alters the adult germ cell methylome. Radford et al. (2014)



- during PGC reprogramming hypomethylation of discrete loci in adult sperm
- enriched for nucleosomes, low methylation
- differential methylation partially resistant to reprogramming but does not persist into next generation
- dysregulated gene expression of neighbouring DMRs in F2 offspring

PGCs
Hypomethylated CpGs
Nucleosome-retaining region

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Imprinting - Parent of origin

- Genomic imprinting is an epigenetic process where certain genes are expressed in a parent - of - origin specific manner.

- Imprinted alleles are silenced such that the genes are either expressed **only** from the non-imprinted allele which is either paternal or maternal.

- This silencing can involve DNA methylation or histone modification to achieve mono-allelic expression.

- The mutant allele that is not expressed – imprinted allele ie PWS paternally imprinted as paternal allele